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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/296,264	04/22/99	WRIGHT J	032396-043

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EXAMINER	
SCHMIDT, M	
ART UNIT	PAPER NUMBER
1635	13

DATE MAILED: 06/19/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/296,264	WRIGHT ET AL.	
	Examiner	Art Unit	
	Mary Schmidt	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 March 2001* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16 and 19-22* is/are rejected.

7)☒ Claim(s) *17 and 18* is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

KATRINA TURNER
PATENT ANALYST

Attachment(s)

15) ☐ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

DETAILED ACTION

1. Claims 1-22 are pending upon entry of Amendment B (Paper 11) filed March 28, 2001.

Claim Rejections - 35 USC § 112

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. Claims 1-5 as amended are newly rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-5 as amended are now drawn broadly to antisense oligonucleotide compositions, or analogs thereof, to any transcribed region of a neuropilin gene from any species. Neuropilin is also known as $VEGF_{165}R$, thus the claims are drawn to antisense to any such $VEGF_{165}R$ gene from any species.

The specification as filed teaches SEQ ID Nos. 1-30 as antisense oligonucleotides to human neuropilin and does not teach antisense to any other species of neuropilin genes although the sequences of rat and mouse neuropilin are disclosed.

One skilled in the art at the time the invention was made would not have been in possession of the invention as broadly claimed. Specifically, one skilled in the art would not have been in possession of antisense oligonucleotides to any neuropilin/$VEGF_{165}R$ gene species as

broadly claimed since neither the specification nor the art teach a representative number of such species of neuropilin/$VEGF_{165}R$ genes from which to design antisense oligonucleotides. Although it was known in the art to one of ordinary skill in the art at the time the invention was made how to design and synthesize antisense oligonucleotides to a known target sequence, it was not known at the time the invention was made what the genus of possible neuropilin/$VEGF_{165}R$ genes embraces, ie. how many are known from a representative number of species. Since the specification as filed only teaches the target neuropilin/$VEGF_{165}R$ gene from human, mouse and rat this is not considered a representative number of species. Murine and human sequences are generally known in the art to have a high sequence homology which usually leads to the rodent and human sequences having a similar function upon expression of the protein. However, other species do not share such an obvious homology to rodent and human species and without further characterization of the expressed protein by function in the host species, can not automatically be assumed to have the same function. As such, the metes and bounds of the structures, ie. the putative sequences, claimed in the genus of any neuropilin/$VEGF_{165}R$ sequence are not clear and one skilled in the art would not have been in possession of any such antisense oligonucleotides, or analogs thereof broadly claimed in claims 1-5 as amended.

4. Claims 5-16 as amended stand rejected and new claims 19-22 are newly rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of inhibiting the growth of the disclosed sequence of human neuropilin in cells in culture and via

injection of the specific disclosed neuropilin antisense sequences which were used in treatment of tumor cells in mice (as in Figure 4), does not reasonably provide enablement for inhibition of any neuropilin gene in any species of whole organism for the therapeutic effects claimed by any antisense having an unspecified length and sequence. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims for the same reasons of record as set forth in the Official Action mailed 09/28/00.

Applicant's arguments filed 03/28/01 have been fully considered but they are not persuasive.

The amendments to claims 5-6, 8, 10, 13, 14 and 16 do not further limit the scope of the claimed invention to methods of administration to cells in culture or to injection in mice of the specifically taught sequences. Claim 5 as noted above, is amended to encompass a broad scope of any nucleic acid to any neuropilin gene from any species and reads on administration of any antisense to any species of neuropilin to any whole organism.

First, in view of the claim amendments, one skilled in the art would necessarily practice undue experimentation to make and use the invention as broadly claimed. Specifically, one skilled in the art would necessarily practice "trial and error experimentation" to design antisense to any possible neuropilin/$VEGF_{165}R$ gene since the genus of possible genes was not known in the art (see the above 35 U.S.C. 112, first paragraph, written description rejection) and the sequences disclosed in the specification as filed do not correlate to any such possible neuropilin/$VEGF_{165}R$

gene sequences as broadly claimed. Further, one skilled in the art would necessarily practice "trial and error experimentation" to use such sequences as pharmaceutical compositions, having implied therapeutic uses, and in the methods claimed which read on whole organism administration of neuropilin antisense to any whole organism. In the previous Official action mailed 09/28/00 it was argued that neither the specification nor the art at the time the invention was made provide sufficient guidance to one skilled in the art how to use any antisense in cells in whole organism because of the unpredictability in the art for therapeutic uses of antisense. Specifically, factors such as routes of administration, concentration of the antisense for effective action in target cells and tissues, modifications of the nucleic acid structure for improved stability *in vivo*, and related issues of non-specific binding and toxicity are all significant factors considered unpredictable in the art. In view of such unpredictability, there is no correlation in the art between the effects observed by one antisense to a particular target to other antisense to a different gene target.

First, Applicants address the scope of claimed neuropilin genes in the claims as amended by citing *In re Vaeck, Amgen Inc. v. Chugai Pharmaceutical Col., Ltd.*, and *Precision Metal Fabricators Inc. V. Jetstreams Systems Co.* to teach that one skilled in the art would have been enabled at the time the invention was made to make and use the invention as claimed. Essentially, these cases are cited to teach that a single embodiment of the claimed genus is acceptable to teach how to make and use the claimed invention.

In response, as argued above, design of an antisense oligonucleotide is dependent on knowing the target sequence from which to test accessible regions. Further, although it is

predictable that by screening one skilled in the art would be able to design at least one functional antisense to a target gene for use *in vitro*, it is not predictable that one skilled in the art would be able to design an antisense to any known target sequence for use in whole organisms. Thus in the case of antisense different levels of unpredictability exist which provide barriers for the use of any possible antisense designed to a known target. These barriers were recited in the previous Official action and summarized above. Thus in some cases, in some inventions, one single embodiment of the species claimed is sufficient to teach one skilled in the art to make and use the claimed invention, but in the instant case, the intricacies of therapeutic uses of an antisense preclude the ability to design a functional antisense for therapeutic uses just by knowing the target gene sequence. Although there are isolated cases in the art where antisense oligonucleotides have gone to clinical trials and indeed have been approved by the FDA for therapeutic use, such results do not correlate to use of other antisense oligonucleotides for therapeutic uses since the nature and scope of the therapeutic effect differs as does the activity of the different antisense based on it's unique sequence in the whole organism.

Applicant further cites other papers known in the art to support the argument that antisense therapy is enabled for one skilled in the art at the time the invention was made. However, for the reasons argued above, the uniqueness of the effects of each different antisense sequence in whole organisms precludes the ability for one skilled in the art to correlate the effects of one antisense to another.

Applicant's arguments therefore do not overcome the *prima facie* scope of enablement rejection.

Note, amendment of the pharmaceutical composition claims to a composition comprising the specific sequence identifier and a pharmaceutically acceptable carrier is considered to overcome the enablement issues for such claims so that only art issues remain.

5. New claims 17 and 18 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

6. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to *Mary M. Schmidt*, whose telephone number is (703) 308-4471.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *John LeGuyader*, may be reached at (703) 308-0447.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group Analyst, *Katrina Turner*, whose telephone number is (703) 305-3413.

M. M. Schmidt
June 17, 2001

ROBERT A. SCHWARTZMAN
PRIMARY EXAMINER